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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/112,840	08/27/93	LUCHERLAPATI	

EXAMINER

18N2/0627

CELL GENESYS, INC.
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ART UNIT	PAPER NUMBER
1804	24

1804
DATE MAILED: 06/27/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 1/26/96

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three (3) month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-12 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1-12 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 23
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

This application should be reviewed for errors.

The suspension of this application is withdrawn in view of the resolution of the potential interference issues and this application is returned to active status.

This Office Action is responsive to the amendment filed January 16, 1996.

Claims 1-12 are active and examined in this Office Action.

The rejection of claims 1-12 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 34-39, 68, 69 and 82 of copending application serial no. 08/031,801 is maintained for reasons of record.

The rejection of claims 1-12 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 29, 30 and 33-35 of copending application serial no. 07/919,297 is maintained for reasons of record.

The rejection of claims 1-6, 8 and 9 under 35 U.S.C. 103 as being unpatentable over Huxley taken with Hooper and Pachnis is maintained for reasons of record. Applicant's arguments are the same as those of record and therefore the rebuttal of record is maintained.

The rejection of claims 7, 10 and 11 under 35 U.S.C. 103 as being unpatentable over Huxley taken with Hooper and Pachnis is maintained for reasons of record. Applicant's arguments are the same as those of record and therefore the rebuttal of record is maintained.

The rejection of claim 12 under 35 U.S.C. 103 as being unpatentable over Huxley taken with Hooper and Pachnis as applied to claims 1-6, 8 and 9 above and further in view of Traver,

Shimizu and Berman is withdrawn. See new ground of rejection under 35 U.S.C. 112, first paragraph, as set forth below.

Applicant's arguments, filed January 16, 1996 have been considered but not found to be persuasive. Applicants have argued that the publication cited by the examiner do not provide a reasonable expectation of success in producing the claimed invention and that the arguments of the Office are drawn to an improper standard. However, applicants have overstated the Office's arguments with respect to the "not impossible standard" and the Office arguments were directed to a further explanation of the basis for the reasonable expectation of success found in the cited references. Applicants have argued that the cited references do not teach that spheroplasts can be fused to ES cells so as to introduce a YAC into an ES cell and that the examiner rebutted the argument by saying that the references don't teach that they can't. Applicants have misconstrued the Office arguments in stating that the examiner has applied an inappropriate standard. As previously stated in prior Office Actions, both a reasonable expectation of success and the motivation to combine the references are provided by the cited prior art, as is required to establish a prima facie case of obviousness. Applicant's arguments, directed to the alleged application of an inappropriate standard, are not persuasive to overcome the rejection.

Applicants have argued that the method of claim 1 has an unexpected advantage and that the unexpected advantage is that the xenogeneic DNA segment containing ES cells produced by the method of claim 1 may be transferred to a blastocyst, wherein the xenogeneic DNA segment is incorporated into the germline of the resultant animal. However, this argument is not persuasive as it is well settled that unexpected results cannot be later argued when none are presented in the specification.

Applicants have argued that the Strauss (Science), Strauss (EMBO) and Bradley publications teach a low probability of producing genetically modified ES cells that can be successfully incorporated into a developing embryo; that these publications teach that the large amount of yeast chromosomal DNA introduced through yeast spheroplast fusion would be likely to interfere with the ability of ES cells to properly differentiate during embryogenesis and that therefore these publications teach away from the claimed invention. However, the argument is not persuasive since Pachnis makes statements indicating a reasonable expectation of success in transferring large segment of mammalian DNA, cloned in YACS, into the mammalian genome: "These results establish that large segments of the mammalian genome, cloned in yeast, can be efficiently transferred into cultured mammalian cells" (Abstract); "In this report we establish that a YAC carrying ~450 kb of human DNA and a neomycin-resistance gene can be transferred efficiently from *S. cerevisiae* cells into mouse fibroblasts (L cells) in culture by cell fusion. In a high percentage of cases the mouse cells contained virtually intact YAC DNA sequences that were stably integrated into the host chromosomes". Regarding ES cells, there is no support for applicant's further speculative assertions that the large amount of yeast chromosomal DNA introduced through spheroplast fusion would be likely to interfere with the ability of ES cells to properly differentiate during embryogenesis since there is evidence in the cited references that large amounts of yeast chromosomal DNA do in fact get integrated into the genome.

Applicants have argued that the office has granted undue weight to a speculative statement in Pachnis. Applicants have argued that Pachnis fails to teach using yeast spheroplasts for fusion to ES cells because Pachnis contains a sentence indicating only that such an experiment should be attempted and fails to

provide a description of the methods for performing the experiments or describe experiments in which ES cells have been modified. However, the argument is not persuasive. Pachnis was cited as reference in a 103 rejection, and not as being anticipatory of the claimed invention. Pachnis discusses the application of the technology applied to L cells and states that the same system ("The application of this YAC transfer system...", page 5113, first column, last paragraph, emphasis added) can be applied to ES cells and that the modifications of the system, such as a choice of a different selectable marker or method of insertion of the selectable marker into the YAC, are obtainable by routine procedures. Contrary to applicant's arguments, Pachnis provides both the motivation and the reasonable expectation of success and does not merely present an "invitation to try". Since Pachnis discloses use of the same transfer system for application to ES cells, Pachnis discloses a sufficient teaching of how to obtain the desired result and assumes that the claimed result would be obtained if the same procedures are followed.

Applicants have argued that the Office has not shown why L and ES cells should be considered equivalent to one another. However, both cell types would be expected to have the same ability to fuse with spheroplasts, lacking evidence to the contrary and secondly, Pachnis states that the same YAC transfer method can be applied to ES cells. The fact that L cells are terminally differentiated and ES cells are totipotent is immaterial to the ability to be fused with YAC spheroplasts according to the method of Pachnis. Pachnis indicates a reasonable expectation of success in producing ES cells by the same method as applied to L cells and obtaining mice produced from those ES cells which carry and transmit any YAC.

Applicants have argued cited Strauss (Science) as evidence that the Pachnis technique would not be expected to work with ES cells. Applicants have further argued that Strauss describes the introduction of purified YACs into L cells by lipid micelles as a desirable alternative to yeast spheroplast fusion because yeast spheroplast fusion and related techniques in which the entire yeast genome is introduced into mammalian cells are considered undesirable because of the mutagenesis that may occur as a result of introduction of a large amount of undesirable yeast DNA that may randomly insert into the mammalian chromosome. However, the instant specification discloses on page 18 that any convenient technique for introducing the DNA into the target cells may be employed and that the techniques include protoplast fusion, e.g., yeast spheroplast:cell fusion, lipofection,electroporation, etc. The specification teaches that any routine method may be used and specifically discloses the use of yeast spheroplast: cell fusion for the practice of the invention. Applicants' arguments that Strauss teaches away from the use of yeast spheroplast:cell fusion because of the possible mutagenic effects of large amounts of yeast genome present as contaminants are not persuasive. Both Pachnis and applicants' own specification provide support for the examiner's position that the yeast spheroplast:cell fusion technique would work and would not be considered "undesirable". The preponderance of evidence supports the examiner's position that Pachnis provides the reasonable expectation of success and that the methods used by Pachnis would result in the claimed invention.

Applicants have argued that the Office argument that there is no problem with the spheroplast technique per se is unsupported and scientifically baseless and there is no way to dissociate the effects of introducing a high level of "junk" DNA from the use of yeast spheroplast fusions because yeast

spheroplasts necessarily comprise "junk" DNA. Applicants have argued that Strauss recognized the problem and sought to avoid it by introducing purified YAC DNA into mammalian cells without the "junk" DNA introduction problem inherent in the spheroplast fusion technique. However, applicant's arguments are not persuasive because the specification teaches that any routine method may be used and specifically discloses the use of yeast spheroplast: cell fusion for the practice of the invention. Contrary to further arguments, Strauss (EMBO) does not teach away from the claimed invention. Applicants' arguments directed to the effect of introducing a large amount of unwanted and uncharacterized yeast genome DNA into an ES cell and that such introduction would be expected to have a deleterious effect on ES cells and cell function is an overstatement and a conclusion improperly drawn from both of Strauss. Strauss (EMBO) states the inclusion "could be mutagenic" and not that it IS mutagenic.

Applicants have argued that the solution proposed by the Office, i.e., to screen more clones, is unwarranted and that the analysis by the Office of the Strauss publication as not teaching away from the use of spheroplasts to transform ES cells is clearly wrong as a matter of law and as a matter of scientific fact. The office disagrees for reasons as stated above. The preponderance of the evidence supports the position that the claimed invention is rendered obvious by the cited prior art and that the prior art, taken with teachings of the instant specification stating that the yeast spheroplast:cell fusion technique is routine and can be used in the practice of the invention, does not teach away from the invention. The specification does not teach unexpected results but in fact specifically states that the yeast spheroplast:cell fusion technique is convenient (routine) and can be used in the practice of the invention.

Applicants have argued that "the office's proposed solution to the problem of transforming the ES cells with yeast spheroplasts as described in the Strauss publication is scientifically incorrect and not supported by any prior art publication". Applicants have argued that by screening a larger number of transfectants, the problem described by the Strauss publication would not be avoided. However, applicants have misunderstood the argument. By screening a larger number of transfectants, the ES cell containing the gene of choice would be determined. The office never said that the screening of increased numbers of cells would be, or could be, capable of differentiating between ES cells transformed solely with YAC DNA and those containing both YAC DNA and yeast genomic DNA. The solution proposed by the Office remains scientifically correct and the concept of screening large number of any type of cells or clones to obtain the desired clone or cell, in this case the ES cell containing the gene of interest, was well within the purview of one of skill in the art.

Applicants have argued that the Office ignores the very reasons that another transformation vehicle is used in the Strauss publications; and that Strauss (Science) teaches that spheroplast fusion with ES cells has never been successful and that lipid micelles should be used instead. However, the arguments regarding the alleged mutagenicity of the yeast genomic DNA have been considered and addressed, above and in the previous Office Action. Applicants have misquoted the text of the Strauss article on page 12, bottom paragraph, and the fact that "spheroplast fusion introduces the whole yeast genome into the transfected cells" is completely unrelated to the next phrase "because DNA injected into mammalian cells is highly mutagenic". Further, the remainder of the quote says "it is possible that the presence of yeast DNA in the transfected ES cells interferes with

their ability to contribute to the germline" and not that the yeast DNA DOES (emphasis added). The office disagrees with applicant's assertions that Strauss (Science) teaches that spheroplast fusion with ES cells has never been successful and that lipid micelles should be used instead. Applicant's further arguments, directed to the screening of additional clones to avoid the problem has been addressed, above.

Applicants have argued that Strauss (Science) teaches that yeast chromosomal DNA is mutagenic irrespective of the manner in which it is introduced into a mammalian cell. Applicants have argued that "it would be apparent to any person of ordinary skill in the art that Strauss (Science) used the term 'injected DNA' as a more convenient grammatical alternative to the cumbersome phrase "spheroplast fusion and microinjected DNA". Contrary to applicant's arguments, the technical procedures required for microinjecting DNA are completely different than those required for spheroplast fusions and microinjections require special equipment not required for spheroplast fusion. Applicants' arguments regarding the equivalence of the terms "spheroplast fusion and microinjected DNA" is a misuse of art recognized terms and a reference clearly demonstrating the equivalent meanings would be of use to resolve the issue.

Applicants have argued that in both cases the DNA is introduced or injected into the cell and the method of introduction does not alter the effects, i.e., the mutagenicity of the unwanted genomic yeast DNA. However, as repeated from above, Strauss merely hypothesizes that the large amount of DNA might have an adverse effect on the function of the ES cell and not that it does. The fact that the specification specifically and clearly states the microinjection and yeast spheroplast:cell fusion are convenient techniques for use in the practice of the

invention further rebuts the arguments regarding the undesirability of the technique.

Applicants' arguments with respect to the meaning of "mutagenic" as it is used in the Strauss publication and the teachings of numerous other publications that yeast genomic DNA is mutagenic are not persuasive. Contrary to applicant's assertions, the office has not misused the term "mutagenic" and secondly, applicants have cited only one other publication, Pavan, as teaching that yeast genomic DNA is mutagenic. The office disagrees with applicant's assessment of the teachings of Pavan; Pavan states that yeast DNA inserted into the mouse genome is a POTENTIAL insertion mutation, and not that it IS a mutation. Applicants have misconstrued the teachings of Pavan. Regarding Gnirke, the fact that Gnirke states that a substantial portion of the yeast genome was maintained in the fusion cell lines along with the YAC does not mean the yeast genome was mutagenic. Gnirke, contrary to arguments, does not state the yeast genomic DNA is mutagenic.

Applicants have argued that Bradley teaches away from the claimed invention since Bradley states that it is unknown whether ES cells modified with YACs will be able to repopulate the germline. However, applicant's assessment of the teachings of Bradley are disputed and the teachings of Bradley are taken as they are written: it is unknown whether cells modified with YACs will be able to repopulate the germline. Bradley cannot fairly be construed as teaching for or against the ability of ES cells modified with YACs to repopulate the germline.

Applicants have argued that the office has failed to weigh the cited publications against one another; that speculative statements in references cited by the office have been irrebuttably presumed to provide a showing of a reasonable expectation of success and that in contrast, every publication

cited by applicants to demonstrate that the prior art teaches away from the claimed invention has been found to be of little weight with determining if a reasonable expectation of success exists. However, the cited publications have been fairly considered as to the teachings as a whole. The preponderance of the evidence as taught by the art, taken together with the teachings of the specification, stating that the yeast spheroplast:cell fusion technique, in addition to other "convenient" techniques can be used in the practice of the invention, render obvious the claimed invention. The specification fails to present unexpected results using the claimed method and Pachnis specifically states that the same method as taught for L cells can be applied to ES cells in order to obtain transgenic mice capable of carrying and transmitting YACs.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for HPRT, does not reasonably provide enablement for a xenogeneic DNA wherein the DNA is a human immunoglobulin gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims. The specification fails to disclose actual working examples of transgenes cloned into YACs wherein the transgene spans the entire human Ig locus and is capable of undergoing isotype

switching. This new ground of rejection is necessitated by the issuance of the patents to Lonberg containing the Cox declaration which states that the human immunoglobulin DNA locus as described in the instant specification was not, and could not, be cloned at the time the claimed invention was made, and secondly, in view of references with significantly later postfiling publication dates specifically stating that isotype switching to downstream isotypes had not yet been achieved using the described human Ig loci contained in YACs.

The Cox declaration states that there were no reports of the cloning in YAC vectors of the region spanning the human delta and gamma3 genes. This region is not readily or predictably cloned and the problem, as explained by the declarant, is possibly due to instability of that region of the human genome in certain cloning vectors, such as YACs. Thus, the art had not reported the cloning of an intact human IgH locus containing the V, D, J, mu, delta and gamma sequences, let alone an intact human IgH locus cloned in a YAC.

The published art was not aware of how to make a transgenic animal containing a transgene capable of undergoing isotype switching to produce human isotypes downstream of IgM as evidenced by Taki et al (1993), disclosing that the authors did not know how to make a transgene that could undergo cis-isotype switching where endogenous sequences were not involved. Morrison, writing a review of the field in Nature (1994), discussed the teachings of Green et al., which referenced two Kucherlapati published PCT applications, (page 812, column 2, bottom):

"In Green and colleague's mice, only the mu heavy chain contributes significantly to the circulating antibody population, and these mice are unable to undergo the isotype switching characteristic of the mature antibody response. But in the mice of Lonberg et al., the heavy-chain locus contains both a mu and gamma1 heavy chain with switch sites, and these authors show that class switching occurs. So they have reconstituted the essential

part of a human-antibody-producing response in a mouse and the system could be used both to study control of antibody production as well as to produce specific human antibodies".

In view of the foregoing, the instant specification was not enabling for the human IgH locus containing the V, D, J, mu, delta and gamma sequences cloned into a YAC nor for a transgenic animal containing the IgH locus-YAC. Regarding claim 12, the specification fails to disclose which of the sequences are necessary to obtain a DNA capable of producing a functional antibody. Although all the claimed regions, i.e., J, D, constant are known in the art, the specification fails to disclose how to operably link the sequences together to obtain a DNA encoding a functional antibody. The specification hypothetically discloses the cloning of an intact human IgH locus containing the V, D, J, mu, delta and gamma sequences into a YAC vector, which as discussed above, was not enabled at the time the claimed invention was made.

The specification of the instant application regarding the actual production of transgenic mice containing human immunoglobulin genes produced by fusion of spheroplasts containing YACs with ES cells is speculative and does not present any working examples showing actual cloning of human immunoglobulins and that if such mice were actually obtained, that human antibodies would be expressed from the the human IgH locus. In view of the lack of actual working examples and evidence presented showing that the DNA containing the human immunoglobulin locus could not be obtained by applicant's method at the time the claimed invention was made, the specification is not enabling for the method, or animals produced by the method, as claimed.

No claim is allowed.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO FAX center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (30 November 15, 1989). The CM1 Fax Center number is (703) 305-3014 or (703) 308-0294.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Suzanne Ziska, Ph.D., whose telephone number is (703)308-1217. In the event the examiner is not available, the examiner's supervisor, Ms. Jacqueline Stone, may be contacted at phone number (703) 308-3153.

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